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Applicant : Fred S. Lamb
Serial No. : 09/512,926
Filed : February 25, 2000

Art Unit : 1617
Examiner : Jennifer M. Kim

Title : METHODS TO REDUCE THE SENSITIVITY OF ENDOTHELIALLY-COMPROMISED VASCULAR SMOOTH MUSCLE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Attached to this facsimile communication cover sheet faxed this 22nd day of April, 2005 to the United States Patent and Trademark Office is a Brief on Appeal.

Respectfully submitted,

Date: April 22, 2005

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Mail Stop Appeal Brief - Patents
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BRIEF ON APPEAL

The Final Office Action for this application was mailed November 30, 2004, and a Notice of Appeal was filed April 14, 2005.

(1) Real Party in Interest

The real party in interest is the University of Iowa Research Foundation.

(2) Related Appeals and Interferences

None.

(3) Status of Claims

Claims 2-5, 12-22, and 24 were previously cancelled. Claims 1, 6-11, 23, and 25 are pending and stand finally rejected.

(4) Status of Amendments

All amendments have been entered.

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(5) Summary of Claimed Subject Matter

The claimed subject matter relates to methods for normalizing the contractile response of vasculature in a patient in need of such normalization, wherein the vasculature has a vascular smooth muscle cell layer and a compromised endothelial cell layer, and wherein the methods include administering a pharmaceutically effective amount of a CLC3 blocker or a pharmaceutically acceptable salt thereof. The claimed subject matter also relates to methods for normalizing the contractile response of vasculature in response to norepinephrine in a patient in need of such normalization, wherein the vasculature has a vascular smooth muscle cell layer and a compromised endothelial cell layer, wherein the method includes administering a pharmaceutically effective amount of a CLC3 blocker or a pharmaceutically acceptable salt thereof.

(6) Grounds of Rejection

(1) That claims 1, 6-11, and 23 are unpatentable over U.S. Patent No. 6,197,789 (the Grainger *et al.* patent). The Examiner stated that the Grainger *et al.* patent teaches the use of tamoxifen to prevent or treat conditions characterized by inappropriate or pathological activity of endothelial cells. The Examiner also stated that the Grainger *et al.* patent teaches the use of tamoxifen to inhibit the activation of endothelial cells associated with vascular surgery, diabetes, hypertension, and coronary artery blockage. The Examiner further stated that the Grainger *et al.* patent teaches that procedural vascular traumas and pathologies such as atherosclerosis, myocardial infarction, and stroke can be prevented by administration of tamoxifen. Thus, the Examiner concluded that it would have been obvious to one of ordinary skill in the art to modify the teaching of Grainger *et al.* and employ tamoxifen to normalize the contractile response of vasculature, since the teaching of "inhibiting contraction" encompasses "normalization," and since the effect of inhibition of contraction of vascular smooth muscle would "normalize" the contraction in patients as disclosed by Grainger *et al.*

(2) That claim 25 is unpatentable over the Grainger *et al.* patent as applied to claims 1, 6-11, and 23 above and further in view of U.S. Patent No. 5,470,883 (the Stromberg patent). The Examiner stated that while the Grainger *et al.* patent does not teach that norepinephrine causes the contractile response of vasculature as set forth in claim 25, the Stromberg patent teaches a

method of inhibiting or reversing the peripheral vasoconstrictive effect of norepinephrine by oral administration of tamoxifen citrate. Thus, the Examiner concluded that it would have been obvious to one of ordinary skill in the art to employ tamoxifen to normalize the norepinephrine-induced contractile response of vasculature comprising a vascular smooth muscle cell layer and a compromised endothelial cell layer, because Stromberg teaches that tamoxifen is useful for reversing (normalizing) the vasoconstrictive effect of norepinephrine and because Grainger *et al.* teach that tamoxifen is useful for treating conditions characterized by inappropriate or pathological activity of vascular smooth muscle cells and endothelial cells.

(7) Argument

Rejection #1: That claims 1, 6-11, and 23 are unpatentable over U.S. Patent No. 6,197,789 (the Grainger *et al.* patent).

(a) The Grainger *et al.* patent does not teach or suggest all elements of the claims.

The Grainger *et al.* patent fails to render claims 1, 6-11, and 23 obvious. First, the Grainger *et al.* patent does not teach or suggest all of the elements of the claims. Specifically, the Grainger *et al.* patent does not suggest using tamoxifen to normalize the contractile response of vasculature having a vascular smooth muscle cell (VSMC) layer and a compromised endothelial cell layer. The Examiner agreed with this assertion, as the Office Action of November 30, 2004 at page 3 states that "Grainger *et al.* do not expressly teach the normalization of contractile response set forth in claim 1."

The Grainger *et al.* patent discloses a therapeutic method for preventing or treating a cardiovascular or vascular indication characterized by a decreased lumen diameter, wherein a therapeutic agent that elevates the level of TGF-β is employed (column 2, line 37 to column 3, line 2 and column 10, lines 44-46). The Grainger *et al.* patent also discloses that such an agent can inhibit the activity of a VSMC, such as proliferation, contraction, and migration (column 17, lines 41-48), as well as inhibit the "pathological" or "abnormal" activity of VSMC (column 3, lines 17-22 and column 6, lines 15-16), defined by Grainger *et al.* as "division, growth or migration of cells occurring more rapidly or to a significantly greater extent than typically occurs in a normally functioning cell of the same type, or in lesions not found in healthy tissues"

(column 7, lines 61-65). The Grainger *et al.* patent does not, however, teach or suggest normalizing the contractile response of endothelially-compromised vascular smooth muscle.

Inhibition of VSMC contraction is not equivalent to normalization of smooth muscle cells. The Merriam-Webster online dictionary defines the term "inhibit" as "prohibit from doing something." *See*, Attachment A submitted to the Patent and Trademark Office (PTO) on February 28, 2005. In contrast, Merriam Webster defines the term "normalize" as "reduce to a norm or standard." *See*, Attachment B submitted to the PTO on February 28, 2005. Figures 2 and 3 of Applicant's specification clearly depict the normalization response by showing that the contractile response of compromised VSM treated with tamoxifen was essentially the same as the contractile response of intact VSM, regardless of whether the intact VSM as treated with tamoxifen. Treatment of compromised VSM with tamoxifen did not prohibit it from having a contractile response; the treatment instead reduced the contractile response to a normal level. Thus, even if the cited art suggested that tamoxifen could inhibit vascular smooth muscle cell contraction, there is nothing in the cited art to suggest that it can correct or normalize the contraction of endothelially-comprised VSMC. Therefore, the Grainger *et al.* patent does not obviate the pending claims.

(b) The Grainger *et al.* patent does not provide motivation to use tamoxifen to normalize contraction of compromised vasculature.

Further, the Grainger *et al.* patent does not provide motivation to use tamoxifen to normalize contraction of compromised vasculature. At no point does the Grainger *et al.* patent provide any evidence to indicate that tamoxifen has an effect on contractile VSMC (*i.e.*, mature, non-proliferative VSMC). A person of ordinary skill in the art would appreciate that contractile and proliferative VSMC serve different purposes, and thus have widely different properties. See, for example, Owens (1995) *Physiol. Rev.* 75:487-517 (reference AQ on the Form 1449 submitted to the Patent and Trademark Office on July 20, 2004). The Owens review teaches that mature VSMC proliferate at an extremely low rate and are almost completely geared for contraction, expressing a unique repertoire of contractile proteins, ion channels, and signaling molecules that clearly distinguish mature VSMC from any other cell type. In contrast, VSMC during vasculogenesis proliferate and produce matrix components of the blood vessel wall, and are not geared for contraction activities. Thus, the Owens review teaches that proliferative and

contractile VSMC are functionally different. The Grainger *et al.* patent discloses only that tamoxifen has an effect on proliferative VSMC. Since the Grainger *et al.* patent fails to provide support for the notion that tamoxifen affects the contractile activity of mature VSMC, a person having ordinary skill in the art reading this reference would not have been motivated to use tamoxifen to normalize vasoconstriction of endothelially-compromised VMSC as recited in the present claims. As such, the Grainger *et al.* patent fails to render the presently claimed methods obvious.

(c) The Grainger *et al.* patent does not provide a reasonable expectation of success for using a compound such as tamoxifen to normalize vasocontraction of compromised vasculature.

Moreover, the teachings of the Grainger *et al.* patent would not have provided a reasonable expectation of success for using a compound such as tamoxifen to normalize vasocontraction of compromised vasculature. The Grainger *et al.* patent fails to provide any evidence that tamoxifen can normalize vasoconstriction. The Grainger *et al.* patent discloses experimental data showing that tamoxifen treatment of VSMC in culture can decrease cell proliferation and increase levels of TGF-beta, while tamoxifen treatment of mice on a high fat diet can reduce the formation of aortic lipid lesions. Thus, the Grainger *et al.* patent is focused on using compounds such as tamoxifen to inhibit proliferation of smooth muscle cells.

Further, Applicant's specification teaches that even after the Grainger *et al.* patent was filed, researchers did not know the effect of tamoxifen on VSM. See, for example, the sections of Applicant's specification at page 2, lines 12-15 and extending from page 26, line 21 to page 27, line 11. These sections disclose that at the time the inventor filed the present application, the inventor believed that tamoxifen treatment would not affect norepinephrine-induced contraction of normal vasculature (*i.e.*, vasculature having an intact endothelium). These sections further disclose that due to the lack of effect on normal VSM, the inventor did not previously examine the effect of tamoxifen on endothelially-compromised VSM. In addition, these sections of the specification disclose that Applicant's previous findings were published as Lamb and Barna (1998) *Am. J. Physiol.* 275:H151-H160, and Lamb and Barna (1998) *Am. J. Physiol.* 275:H161-H168 (both included on the Form 1449 mailed to the Patent and Trademark Office on June 18, 2001). Thus, as of 1998, the effect of tamoxifen on normal VSM was uncertain. Due to this uncertainty, a person of ordinary skill reading the Grainger *et al.* patent would not have had a

reasonable expectation that tamoxifen would normalize the contractile response of vasculature having a compromised endothelial layer.

In conclusion, since the Grainger *et al.* patent fails to teach or suggest all of the elements recited in the claims, and fails to provide either motivation or a reasonable expectation of success for using tamoxifen to normalize vasocontraction of compromised VSM, it does not render the present claims obvious. In light of the above, Applicant respectfully requests reversal of the Examiner's rejection of claims 1, 6-11, and 23 under 35 U.S.C. § 103(a).

Rejection #2: That claim 25 is unpatentable over the Grainger *et al.* patent as applied to claims 1, 6-11, and 23 and further in view of U.S. Patent No. 5,470,883 (the Stromberg patent).

Claim 25 recites a method to normalize the contractile response of vasculature in response to a vasoconstrictor agonist in a patient in need of such normalization. The cited patents fail to suggest such a method. As discussed above, "inhibiting" contraction is not the same as "normalization" of contraction. Neither the Grainger *et al.* patent nor the Stromberg patent suggests using tamoxifen to normalize the contractile response of vasculature in response to a vasoconstrictor agonist such as norepinephrine. In fact, the Office Action mailed on March 23, 2004, by which time both the Grainger *et al.* patent and the Stromberg patent were of record, included the following statement by the Examiner at pages 4 and 5:

> . . . there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to normalize the response to any vasoconstrictor (emphasis in original) . . . given the lack of . . . prior art regarding normalizing in response to a vasoconstrictor agonist (emphasis added) . . .

Given these statements, the Examiner appeared to believe, at least as of March 2004, that the prior art failed to teach or suggest using an agent such as tamoxifen to normalize contraction in response to a vasoconstrictor such as norepinephrine, as recited in claim 25. Since neither the Grainger *et al.* patent nor the Stromberg patent suggests using tamoxifen to normalize contraction, the combination of these references fails to render claim 25 obvious.

In light of the above, Applicant respectfully requests reversal of the Examiner's rejection of claim 25 under 35 U.S.C. § 103(a).

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Please apply $250 for the brief fee, as well as any other charges or credits, to Deposit Account No. 06-1050.

Respectfully submitted,

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Appendix of Claims

1. A method to normalize the contractile response of vasculature in a patient in need of such normalization, the vasculature comprising a vascular smooth muscle cell layer and a compromised endothelial cell layer, wherein the method comprises administering a pharmaceutically effective amount of a CLC3 blocker, or a pharmaceutically acceptable salt thereof.

6. A method of claim 23, wherein the compound administered is 1-p-β-dimethylaminoethoxyphenyl-trans-1,2-diphenylbut-1-ene, or a pharmaceutically acceptable salt thereof.

7. A method of claim 23, wherein the patient has diabetes.

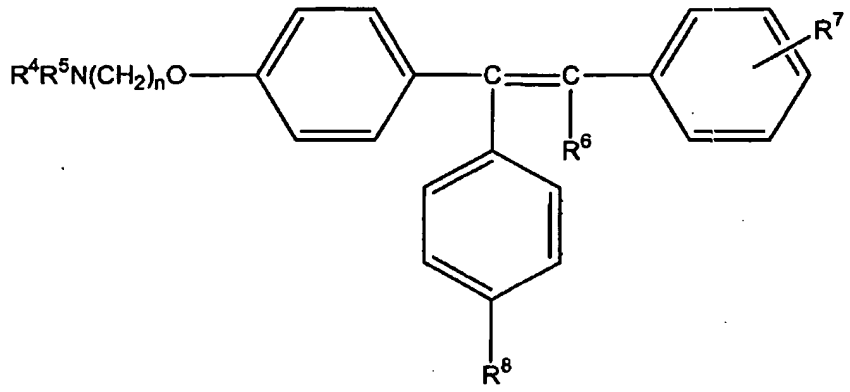
8. A method of claim 23, wherein the patient has had a surgical procedure.

9. A method of claim 23, wherein the patient has hypertension.

10. A method of claim 23, wherein the patient has coronary artery disease.

11. A method of claim 23, which further comprises administering a pharmaceutically-effective compound selected from the group consisting of: an anti-diabetes agent; an anti-hypertension agent; an anti-coronary artery disease agent; and an anti-restenosis agent.

23. A method of claim 1, wherein the CLC3 blocker is a compound of Formula I .



wherein

either R^4 is H or a lower alkyl radical and R^5 is a lower alkyl radical, or R^4 and R^5 are joined together with the adjacent nitrogen atom to form a heterocyclic radical;

R^6 is H or a lower alkyl radical;

R^7 is H, halo, OH, a lower alkyl radical, or is a buta-1,3-dienyl radical which together with the adjacent benzene ring forms a naphthyl radical;

R^8 is H or OH; and

n is 2;

or a pharmaceutically acceptable salt thereof.

25. A method to normalize the contractile response of vasculature in response to a vasoconstrictor agonist in a patient in need of such normalization, the vasculature comprising a vascular smooth muscle cell layer and a compromised endothelial cell layer, wherein the method comprises administering a pharmaceutically effective amount of a CLC3 blocker, or a pharmaceutically acceptable salt thereof, and wherein the vasoconstrictor agonist is norepinephrine.